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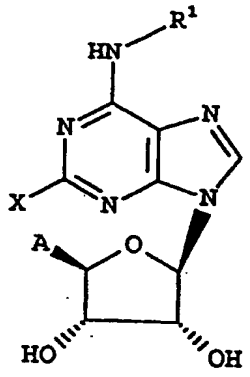
(54) Title: CHEMICAL COMPOUNDS, THEIR PREPARATION AND USE

(57) Abstract

A compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein X is halogen, amino, perhalomethyl, cyano, C_{1-6}-alkoxy, C_{1-6}-alkylthio or C_{1-6}-alkylamino; A is methyl, halomethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl; R^1 is selected from optionally substituted *N*-bonded heterocyclics. The compounds have been found useful for treating central nervous system ailments.



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Chemical Compounds, their Preparation and Use

The present invention relates to therapeutically active *N*-substituted 5'-deoxy adenosine derivatives further substituted at the 2- and 5' positions and pharmaceutically acceptable addition salts thereof, and their pharmaceutical compositions as well as methods for using the compounds and compositions described.

Background of the Invention

Adenosine is a naturally occurring purine nucleoside, from which is derived a range of agonists at adenosine receptors having considerable potential in the treatment of human disease (Life Sciences, **1991**, *49*, 1435-1453; Journal of Medicinal Chemistry, **1992**, *35*, 407-422; Annual Reports in Medicinal Chemistry, **1993**, *28*, 295-304).

Adenosine has been shown to have a number of significant effects on the mammalian central nervous system (CNS) (Annual Reports in Medicinal Chemistry, **1988**, *23*, 39-48; Adenosine in the Nervous System, T.W. Stone, Ed., Academic Press Ltd., London 1991) especially under conditions of neuronal stress where the compound appears to act as an endogenous neuroprotectant (Progress in Neurobiology, **1988**, *31*, 85-108, Trends in Pharmacological Sciences, **1992**, *11*, 439-445). For example, the concentration of adenosine has been demonstrated to rise greatly in certain brain regions following epileptic seizures or conditions of neuronal ischaemia/anoxia (Brain Research, **1990**, *516*, 248-256).

It has been established for some years now that centrally acting adenosine receptor agonists or compounds which increase extracellular adenosine levels can exhibit what is termed neuromodulator activity

(Trends in Neurosciences, **1984**, 164-168). Such substances influence the release of neurotransmitters in regions of the central nervous system (Annual Review of Neuroscience, **1985**, *8*, 103-124; Trends in Neurosciences, **1984**, 164-168), with particular inhibitory effects on the release of the excitatory amino acid glutamic acid (glutamate) in the CNS (Nature, **1985**, *316*, 148-150) especially under ischaemic conditions (Journal of Neurochemistry, **1992**, *58*, 1683-1690).

There are several CNS ailments for which this adenosine receptor mediated neuromodulator activity is accepted by persons skilled in the art as being of clear therapeutic benefit including the treatment of convulsive disorders (European Journal of Pharmacology, **1991**, *195*, 261-265; Journal of Pharmacology and Experimental Therapeutics, **1982**, *220*, 70-76; European Journal of Pharmacology, **1993**, *242*, 221-228), prevention of neurodegeneration under conditions of brain anoxia/ischaemia (Neuroscience Letters, **1987**, *83*, 287-293; Stroke, **1988**, *19*, 1133-1139; Neuroscience, **1989**, *30*, 451-462; Pharmacology of Cerebral Ischaemia 1990, (Kriegelstein, J. and Oberpichler, H., Eds., Wissenschaftliche Verlagsgesellschaft mbH: Stuttgart, **1990**, pp 439-448; Trends in Pharmacological Sciences **1992**, *11*, 439-445) or the use of a purinergic agent in the treatment of pain (European Journal of Pharmacology, **1989**, *162*, 365-369; Neuroscience Letters, **1991**, *121*, 267-270).

Adenosine receptors represent a subclass (P_1) of the group of purine nucleotide and nucleoside receptors known as purinoreceptors. This subclass has been further classified into distinct receptor types which have become known as A_1, A_2 and A_3. Extensive research has been carried out in a quest to identify selective ligands at these sites. Selective ligands exist for A_1, A_2 and A_3 adenosine receptors and the structure-activity relationships of the various reference ligands have been reviewed

(Comprehensive Medicinal Chemistry, Volume 3, (Hansch, C., Sammes, P.G. and Taylor, J.B., Eds., Pergamon Press PLC: **1990**, pp 601-642, Journal of Medicinal Chemistry, **1994**, *37*, 636 - 646). Among the known adenosine receptor agonists most selective for the A_1 receptor over the A_2 receptor are the examples where the adenine nucleus is substituted with a cycloalkyl group on the amino function, for example *N*-cyclopentyladenosine (CPA) and *N*-cyclohexyladenosine (CHA) (Journal of Medicinal Chemistry, **1985**, *28*, 1383-1384) or 2-chloro-*N*-cyclopentyladenosine (CCPA) (Naunyn-Schmiedeberg's Arch. Pharmacol. **1988**, *337*, 687-689).

There is evidence for further subdivision of adenosine receptors into the subtypes A_{2a}, A_{2b} (of high and low affinity) A_3 and A_4. The latest status of these subtypes has been reviewed (Drug Development Research, **1993**, *28*, 207-213; Trends in Pharmacological Sciences 1993, 290-291; Pharmacological Reviews, **1994**, *46*, 143-156). The A_3 receptor (Proceedings of the National Academy of Sciences of the USA, **1992**, *89*, 7432-7436; Trends in Pharmacological Sciences, **1994**, *15*, 298-306) appears to be responsible for some of the cardiovascular effects of reference ligands (British Journal of Pharmacology, **1993**, *109*, 3-5).

Various examples of *N*-heteroarylalkyl substituted A_1 selective adenosine analogues have been reported in the literature. It should be noted that some of these are named as $\underline{N}^6$-substituted adenosine derivatives, but this is equivalent to ACS-approved nomenclature where compounds substituted on adenosine's 6-amino position are referred to as *N*-substituted adenosine derivatives. Derivatives of adenosine with the heteroatoms sulphur, oxygen or nitrogen bonded directly to the 6-amino substituent are not common in the chemical literature, but those cases known are summarised below.

Derivatives with hydrogen at the purine 2-position include *N*-aminoadenosine, *N*-[(*N*-methyl-*N*-phenyl)amino]adenosine, *N*-hydroxyadenosine, *N*-methoxyadenosine and *N*-benzyloxyadenosine (Journal of Medicinal Chemistry, **1985**, *28*, 1636-1643); *N*-ethoxyadenosine (Chemical and Pharmaceutical Bulletin, **1973**, *21*, 1676-1682; *ibid.*, **1973**, *21*, 1835-1838); *N*-(methylamino) adenosine and *N*-[(*N*-hydroxy-*N*-methyl)-amino]adenosine (Journal of Medicinal Chemistry, **1968**, *11*, 521-523). A range of compounds which have no further substitution on the ribose moiety have been been published by Novo Nordisk (Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666).

Examples of adenosine derivatives with oxygen or nitrogen atoms bonded to the 6-amino substituent, containing an additional purine 2-substituent are 2-amino-*N*-hydroxyadenosine (Journal of Medicinal Chemistry, **1972**, *15*, 387-390); 2-amino-*N*-aminoadenosine (Chemical and Pharmaceutical Bulletin, **1969**, *17*, 2373-2376); 2-amino-*N*-methoxyadenosine (Chemical and Pharmaceutical Bulletin, **1975**, *23*, 464-466); 2-chloro-*N*-hydroxyadenosine (Journal of Medicinal Chemistry, **1991**, *34*, 2226-2230), 2-fluoro-*N*-hydroxyadenosine and 2-fluoro-*N*-aminoadenosine (Journal of Medicinal Chemistry, **1970**, *13*, 427-430) and 2-fluoro-*N*-methoxyadenosine (Journal of Medicinal Chemistry, **1971**, *14*, 816-819). These articles involve compounds with intact ribose moieties.

In the above scientific articles, no mention is made of any pharmacological effects of the compounds concerned on the central nervous system.

There are also very few examples of compounds designed as adenosine receptor agonists where the ribose moiety in adenosine is chemically modified, and many of those known have poor affinity for the adenosine receptor (Journal of Medicinal Chemistry, **1986**, *29*, 346-353). How-

ever, minor modifications at the 3'- and 5'-positions appear to be allowed and amongst these the 5'-chloro-5'-deoxy adenosines show particularly good receptor affinity (Journal of Medicinal Chemistry, **1989**, *32*, 8-11). Other scientific articles also describe 5'-modifications of adenosine derivatives (Journal of Medicinal Chemistry, **1986**, *29*, 1683-1689).

EP Publications No. 181,128 and 181,129 disclose 5'-deoxy adenosine derivatives containing 5'-hydrogen, 5'-halogen and 5'-methylthio, which are claimed to have desirable antiinflammatory, analgesic as well as CNS and antihypertensive properties respectively. EP Publication No. 232,813 discloses *N*-substituted adenosines including a larger range of 5'-modified compounds which are also claimed to have desirable CNS and antihypertensive properties. PCT Publication WO 94/02497 reveals certain sulphohydrocarbon derivatives of adenosine, where the possibilty exists for substitution at the 5'-position of the ribose moiety.
In PCT Publication WO 88/03147 5'-substituted adenosine derivatives with selectivity for the adenosine A2 receptor are disclosed.

In US Patent No. 4,962,194 methods for preparing 5', *N*-disubstituted adenosine derivatives are revealed. GB Patent No. 1,101,108 discloses 5', *N*-disubstituted adenosine analogues which possess cardiovascular activity. US Patent No. 3,910,885 reveals 4'-alkoxy and 4'-haloalkoxy nucleosides. PCT Publication WO 94/06348 discloses a number of pyrrolo[3,4-d]pyrimidine structures which are formally isosteric with adenosine and which are modified with substituents at the sugar 5'-position. US Patent No. 5308837 covers the use of 5'-amine substituted adenosine analogues as immunosuppressants.

In US Patent No. 3,819,613, substituted adenosine analogues with hydrazone derivatives on the 6-amino function are disclosed as

hypotensive agents. In GB Patent No. 1,351,501, adenosine and 2-aminoadenosine derivatives having a -NH-R_2 group joined to the 6-amino function are disclosed as coronary dilators and platelet aggregation inhibitors. In EP Publication No. 152,944, a series of 2-, 6- and 8-substituted adenosine derivatives are described having activity as anti-allergy agents. In EP Publication No. 253,962, adenosine and 2-halo-adenosine analogues having an alkyl, cycloalkyl or an aralkyl group attached to the 6-amino function are described with activity as anti-dementia agents.

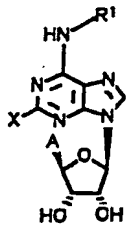
In EP Publication No. 402,752, derivatives of adenosine unsubstituted in the 2-position are described which have a substituted heteroaromatic 1-pyrrolyl moiety attached to the 6-amino group. In PCT Publication No. WO 91/04032, methods of preventing neural tissue damage in neuro-degenerative diseases by increasing extracellular concentrations of adenosine are described. Examples are given of prodrug esters of AICA riboside which are claimed to be centrally acting neuroprotective agents. In PCT Publication No. WO 92/02214, analogues of AICA riboside are described which increase extracellular adenosine levels with beneficial effects claimed in peripheral and CNS ischaemia. In PCT Publication No. WO 90/05526, 2-(alkylalkynyl)adenosine derivatives are described for treatment of ischaemic disease of the heart and brain. In EP Publication No. 423 777 a method for treating gastrointestinal motility disorders using N(6) (substituted aminoalkyl) adenosine derivatives is disclosed. EP Publication No. 490 818 describes a new use of 2'-*O*-methyl adenosine derivatives for a range of ailments including neurodegenerative disorders.

The present invention relates to new adenosine analogues with modified ribose moieties which show potent binding *in vitro* to the adenosine A1 receptor, and which also display selectivity for A_1 receptor binding *in vitro* over that to the A_2 receptor subtype. In addition, the compounds

contained in this invention have a relatively high lipophilicity, especially when compared to adenosine analogues which are not substituted on the 6-amino group or the purine 2-position. This latter property makes these compounds suitable for passage across the blood brain barrier.

The compounds are also substrates for nucleoside-specific active transport systems into the CNS across the blood barrier. These useful properties support the notion that the compounds are candidate drugs for treatment of the CNS ailments mentioned within this invention in humans as well as cardiovascular disorders such as cardiac ischaemia.

The compounds of the invention are purine derivatives of formula I, or a pharmaceutically acceptable salt thereof:



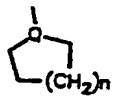
(I)

wherein

X is halogen, amino, perhalomethyl, cyano, C_{1-6}-alkoxy, C_{1-6}-alkylthio or C_{1-6}-alkylamino;

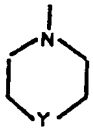
A is methyl, halomethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

R^1 is selected from the groups consisting of



(a)

wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylsulphinyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, phenylthioalkyl or



(b)

wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,
wherein Y is oxygen;
R^2 is C_{1-6}-alkyl;
R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;
R^4 is C_{1-6}-alkyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy.

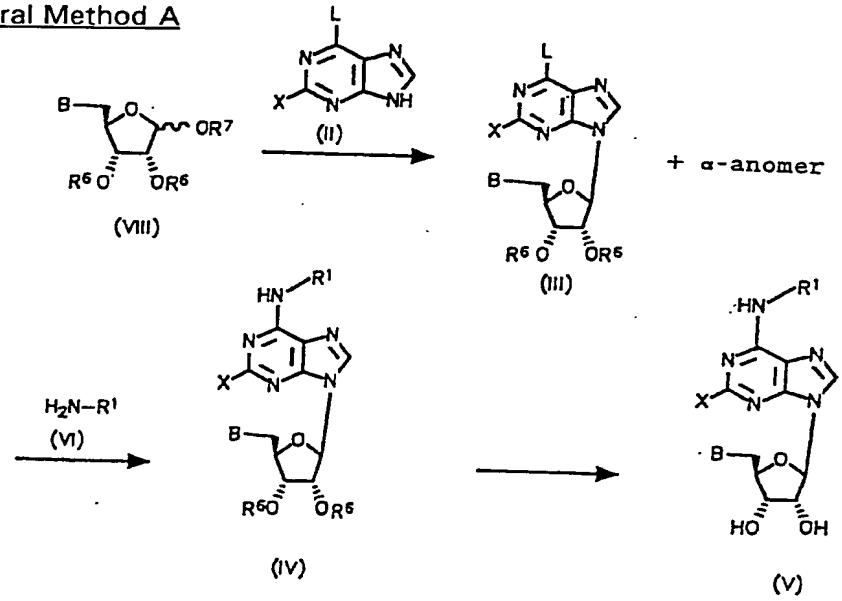
In certain examples, the group R^1 can contain one or more asymmetric carbon atoms in addition to those asymmetric centres already present in the molecule. In examples where this is the case, this invention includes all resulting diastereoisomers and mixtures thereof.

Various salts of compounds of formula (I) can be prepared which is physiologically acceptable. These include addition salts derived from inorganic or organic acids, for example, acetates, fumarates, glutarates, glutaconates, lactates, maleates, methanesulphonates, phosphates, salicylates, succinates, sulphates, sulphamates, tartrates and para-toluenesulphonates. In some cases, solvates of either the free nucleosides or the acid addition salts can be isolated and these solvates may, for example, be hydrates or alcoholates.

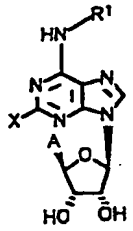
Compounds of formula (I), which act as adenosine receptor agonists, are useful in the treatment of central nervous system conditions such as anxiety, neuronal ischaemia/anoxia, convulsive disorders (epilepsy) and neurodegeneration (including Parkinson's disease) in humans. This includes treating disorders where the blood flow to the brain is interrupted, for example during traumatic head injury, cardiac arrest and stroke. Further, the compounds of formula (I) are useful as analgesic agents, in lowering plasma free fatty acid (FFA) levels or as cardiovascular agents, e.g. treatment of myocardial ischaemia.

The compounds according to the invention are prepared as follows:

General Method A



A compound of general formula (V) may be prepared by reacting a substance of general formula (VIII) (prepared according to general method B), where B represents a hydrogen, a halogen, a pseudohalogen, an alkoxy, or a thioalkoxy group and R^6 and R^7 represent hydrogen or a hydroxyl protecting group such as benzoyl, p-toluyl, lower alkanoyl, an alkylated silyl group, or alternatively the two R^6 may together represent a 1-methylethylidene with R^7 being defined as above, with a purine derivative (II) where X and L each represents a halogen, an alkoxy or a thioalkoxy group or a (protected) amino group, giving the reaction product (III) alone or together with the corresponding α-anomer. Substitution of L in compound (III) with an alkylated amine, an alkylated hydroxylamine or a functionalised hydrazine of general formula (VI) will give compound (IV). The corresponding α-anomer of compound (III) may be reacted in a similar way. Depending upon the nature of group R^6 deprotection of a compound of formula IV can be performed according to the art known (Greene, T.W., Protective Groups in Organic Synthesis, 2nd ed., **1991**), to give a compound of formula V, which is a compound of formula I,

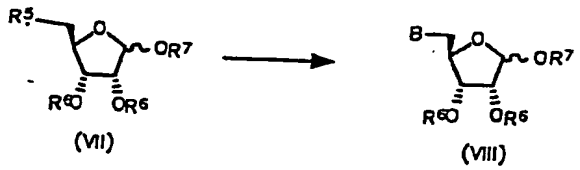


(I)

wherein A is methyl, chloromethyl, fluoromethyl, cyanomethyl, amino-

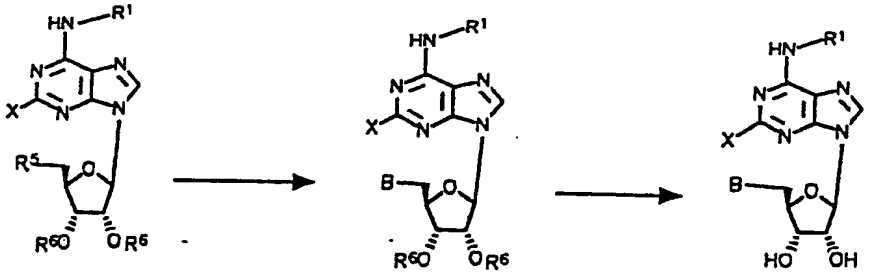
methyl, methylthiomethyl or methoxymethyl.

General Method B:



A compound of formula (VIII) where B, R^6 and R^7 are defined as in general method A, can be prepared from a compound (VII), where R^6 and R^7 are defined as in formula (I) and R^5 represents a hydroxy group or a suitable leaving group such as a halogen or a halogenated sulphonate. In cases where R^5 represents a hydroxy group, this can be directly alkylated to an alkoxy group with an alkylating reagent, or it can be halogenated with a suitable halogenation reagent to give compound (VIII). Alternatively, the group B may be introduced by reacting a compound (VII) where R^5 represents a leaving group, with a nucleophilic reagent containing nucleophiles such as an alkoxide, thioalkoxide, or halide (incl. pseudo-halides). In cases where B represents a hydrogen, this may be introduced by reduction of compound (VII) where R^5 represents a hydroxyl or a suitable leaving group with a reducing reagent. The protecting groups R^6 and R^7 can be removed as described (Greene, T.W., Protective Groups in Organic Synthesis, 2nd ed. 1991).

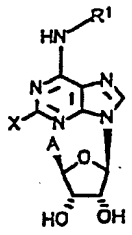
General Method C:



(IX) (X) (V)

A compound of formula (V) where B, X and R^1 are defined as in general method A, can be prepared from a compound (IX) where R^6 is defined as in formula (VIII) and R^5 represents a hydroxy group or a suitable leaving group such as a halogen or an halogenated sulphonate. In cases where R^5 represents a hydroxy group this can be directly alkylated to an alkoxy group with an alkylating reagent, or it can be halogenated with a suitable halogenation reagent to give compound (X). Alternatively, the group B may be introduced by reacting a compound (IX) where R^5 represents a leaving group with a nucleophilic reagent containing nucleophiles such as an alkoxide, thioalkoxide, or halide (incl. pseudohalides).

In cases where B represents a hydrogen this may be introduced by reduction of compound (IX) where R^5 represents a hydroxyl or a suitable leaving group, with a reducing reagent. The protecting groups R^6 of formula (X) can be removed as described in the art known (Greene, T.W., Protective Groups in Organic Synthesis, 2nd ed **1991**), to give a compound of formula V, which is a compound of formula I,



(I)

wherein A is methyl, chloromethyl, fluoromethyl, cyanomethyl, aminomethyl, methylthiomethyl or methoxymethyl.

Methods for assessing adenosine receptor binding *in vitro* have been reviewed [Adenosine Receptors, Cooper, D.M.F. and Londos, C., Eds., Alan R. Liss, Inc.: New York, **1988**, 43-62].

Evaluation of these compounds in established animal models has indicated that the compounds according to the invention possess desirable central nervous system properties. For example, they act as anticonvulsant agents, are effective in animal models of pain, and show cerebroprotective effects in laboratory test animals subjected to simulated cerebral ischaemia. In addition, the compounds may have efficacy as neuroprotective agents in cases of cerebral oedema and traumatic head injury.

Evaluation of *in vitro* binding to adenosine A_1 and A_2 receptors.

The affinity of the novel compounds described in this invention for the adenosine A_1 receptor was determined essentially as described in the literature using [^{3}H]-*R*-PIA as a radioligand (Naunyn-Schmiedeberg's Archives of pharmacology, **1980**, *313*, 179-187). Affinity for the A_2 receptor was measured using the radioligand [^{3}H]-CGS 21680 (European Journal of Pharmacology, **1989**, *168*, 243-246), and the values for representative compounds is given in the table below. *In vitro* receptor

binding values obtained for the reference standards CPA [*N*-(cyclopentyl)adenosine] and *R*-PIA [(R)-*N*-(1-phenyl-2-propyl)adenosine]) are included for comparison. The methods both for the above *in vitro* examination of the compounds and the method used for DMCM-induced seizures *in vivo* are summarized in the European Journal of Pharmacology, **1993**, *224*, 221-228.

The results obtained by testing selected compounds disclosed in the present invention are shown in the table I.

TABLE I

Adenosine agonist tested	A_1 Receptor Binding (Ki, nM)	A_2 Receptor Binding (Ki, nM)	Ratio A_2/A_1	DMCM-ind. seizures (ED_{50}, mg/kg)
Example 1	6.4	2739	428	0.4
Example 11	11	6600	600	4.7
Example 12	74	4655	63	6.1
Example 18	5.3	2420	457	1.0
CPA	1.2	192	77	0.2
R-PIA	1.9	116	61	0.5

The compounds of the invention, together with a conventional adjuvant, carrier or diluent, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets of filled capsules, or liquids, such as

solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral use (including subcutaneous administration and infusion). Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the adenosine receptor agonist commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparation, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteri-

ously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir or the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0 mg
Lactosum	67.0 mg Ph.Eur.
Avicel™	31.4 mg
Amberlite™IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Owing to activity against pain or convulsive disorders and prevention of neurodegeneration under conditions of anoxia/ischaemia the compounds of the invention are extremely useful in the treatment of related symptoms in mammals, when administered in an amount effective for agonist activity of compounds of the invention. The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of adenosine receptor agonist, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulphate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective amount of adenosine receptor agonist, and in any event an amount which is effective for the treatment of anoxia, traumatic injury, ischemia, migraine or other pain symptoms, epilepsy, or neurodegenerative diseases owing to their adenosine receptor agonist activity. Suitable dosage ranges are 1-200 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The preparation of compounds of formula (I) is further illustrated in the following examples.

Hereinafter, TLC is thin layer chromatography, THF is tetrahydrofuran, TFA is trifluoracetic acid and mp is melting point. Where melting points

are given, these are uncorrected. The structures of the compounds are confirmed by assignment of NMR spectra (from which representative peaks are quoted) and by microanalysis where appropriate. Compounds used as starting materials are either known compounds or compounds which can be prepared by methods known *per se*. Column chromatography was carried out on Merck silica gel 60 interfaced via a system module to a Waters 490 multiwavelength detector to a reversed phase C18 column (250 x 4 mm, 5μm, 100Å; eluent flow rate 1 mL/ min at 35°C). Retention times are given in minutes.

EXAMPLE 1

2,5'-Dichloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

The title compound was prepared according to general method C.

2,5'-Dichloro-5'-deoxy-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)-adenosine

2-Chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine [prepared by protection of 2-Chloro-*N*-(1-piperidinyl)adenosine (Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666)] (0.28 g, 0.47 mmol), triphenylphosphine (0.31 g, 1.18 mmol) and tetrachloromethane (0.18 g, 1.18 mmol) was stirred in dry dimethylformamide (10 ml) at 20°C for 48 h. The reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (95:5) to give 2,5'-dichloro-5'-deoxy--2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine (0.10 g, 48%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.34 (3H, s, -CH_3), 1.36 (2H, m, piperidine C-H), 1.62 (4H, m, piperidine C-H), 2.82 (4H, br, piperidine C-

H), 3.78, 3.88 (2H, ABX, H-5′$_a$ and H-5′$_b$), 4.35 (1H, ddd, H-4′), 5.02 (1H, dd, H-3′), 5.39 (1H, dd, H-2′), 6.20 (1H, d, H-1′), 8.36 (1H, s, H-8). HPLC retention time 21.45 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

Deprotection of 2,5′-dichloro-5′-deoxy-2′,3′-*O*-(1-methylethylidene)-*N*--(1-piperidinyl)adenosine (0.11 g, 0.25 mmol) was performed by dissolving the compound in a mixture of ethanol (5 ml) and sulphuric acid (0.2M, 5 ml) and stirring the mixture for 72 h. at room temperature. The reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with dichloromethane (3 x 50 ml). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and 10% ammonia solution in ethanol (9:1), to provide the title 2,5′-dichloro-5′-deoxy-*N*-(1-piperidinyl)adenosine (0.1 g, 99%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.35 (2H, br, piperidine C-H), 1.62 (4H, br, piperidine C-H), 2.80 (4H, br, piperidine C-H), 3.82, 3.93 (1H, ABX, H-5′$_a$ and H-5′$_b$), 4.10 (1H, dd, H-4′), 4.18 (1H, dd, H-3′), 4.63 (1H, dd, H-2′), 5.88 (1H, d, H-1′), 8.39 (1H, s, H-8). HPLC retention time 10.95 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99% purity at 250 nm).

EXAMPLE 2

(S)-2,5′-Dichloro-5′-deoxy-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine

The title compound was prepared according to general method C. (S)-2-Chloro-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine [Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666] (0.35 g, 0.8 mmol) was dissolved in acetonitrile (5 ml) and cooled on an ice-water bath. Under a

nitrogen atmosphere, thionyl chloride (0.34 g, 0.2 ml, 2.4 mmol) (see Borchardt, R.T., Huber, J.A. and Wu, Y.S., Journal of Organic Chemistry, **1976**, *41*, 565-567) was added and a precipitate appeared which dissolved over the following 15 min. Pyridine (0.13 ml, 0.13 g, 1.6 mmol) was introduced gradually, the reaction mixture became yellow in colour and was allowed to reach room temperature gradually. After stirring the mixture overnight, ice was added and the reaction mixture was neutralised to pH 7 with aqueous sodium bicarbonate prior to extraction with ethyl acetate (2 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated to provide the intermediate 2,3-*O*-sulphinyl derivative (0.35 g), to which was added methanol (5 ml), water (1 ml) and 25% aqueous ammonia solution (0.25 ml) and this mixture was stirred for 16 h. The solution was evaporated in vacuo, and the resultant residue was purified by flash chromatography on silica gel eluting with a mixture of dichloromethane and 10% ammonia in ethanol (17:3), to provide the title (S)-2,5'-dichloro-5'-deoxy-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine (0.12 g, 34%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.50 - 1.60 (1H, br, pyrrolidine C-H), 1.78 (2H, br q, pyrrolidine C-H), 1.92 - 2.03 (1H, br, pyrrolidine C-H), 3.85, 3.95 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, br dd, H-4'), 4.17 (1H, dd, H-3'), 4.67 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.34 (1H, br s, -NH). HPLC retention time 9.65 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99% purity at 250 nm).

$C_{16}H_{22}Cl_2N_6O_4$. 0.25 H_2O requires C, 43.9; H, 5.2; N, 19.2. Found: C, 43.7; H, 5.4; N, 19.4%.

EXAMPLE 3

2,5'-Dichloro-5'-deoxy-*N*-(4-phenoxy-1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(4-phenoxy-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (0.5 g, 1.05 mmol) was subjected to the chlorination conditions described above, providing the title compound 2,5'-dichloro-5'-deoxy-*N*-(4-phenoxy-1-piperidinyl)adenosine which precipitated on treatment with dichloromethane following trituration with ether. Drying in vacuo provided a solid (0.28 g, 56%), m.p. 165-170°C, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.74 - 1.84 (2H, br, piperidine C-H), 1.99 - 2.08 (2H, br, piperidine C-H), 2.80 - 2.90 (2H, br, piperidine C-H), 3.04 - 3.12 (2H, br, piperidine C-H), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.44 (1H, br, PhO-C-H) 4.66 (1H, dd, H-2'), 5.50, 5.63 (2H, 2d, 2'- and 3'-OH), 5.89 (1H, d, H-1'), 6.94 (1H, t, Ar-H), 6.99 (2H, d, Ar-H), 7.30 (2H, t, Ar-H), 8.40 (1H, s, H-8). HPLC retention time 19.15 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99.9% purity at 250 nm).

EXAMPLE 4

2,5'-Dichloro-5'-deoxy-*N*-(3-methoxy-1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(3-methoxy-1-piperidinyl)adenosine (prepared by *O*-methylation of *N*-tertbutyloxycarbonyl-3-hydroxypiperidine, followed by use of the *N*-amination technique described in Overberger, C.G. and Herin, L.P. Journal of Organic Chemistry, **1962**, *27*, 417, and further reaction of the resultant hydrazine as described in Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) (0.1 g, 0.24 mmol) was subjected to the chlorination conditions described in Example 2, providing the title 2,5'-dichloro-5'-deoxy-*N*-(3-methoxy-1-piperidinyl)adenosine (mixture of diastereoisomers) (0.07 g, 67%), following column chroma-

tography, as a solid, m.p. 200 - 202°C. ^{1}H-NMR (400MHz, DMSO-d_6) δ 3.86, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.11 (1H, q, H-4'), 4.19 (1H, q, H-3'), 4.65 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.88 (1H, d, H-1'), 8.39 (1H, s, H-8). HPLC retention time 17.08 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 98.7% purity at 250 nm).

EXAMPLE 5

2,5'-Dichloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(4-phenylthio-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (5.49 g, 11.1 mmol) was subjected to the reaction conditions described above, providing the title 2,5'-dichloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine which precipitated from the aqueous methanolic ammonia. Recrystallization provided a solid (3.93 g, 69%), m.p. 154 - 157°C, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.74 - 1.84 (2H, br, piperidine C-H), 1.95 - 2.05 (2H, br, piperidine C-H), 2.80 - 2.90 (1H, br, piperidine C-H), 3.04 - 3.12 (2H, br, piperidine C-H), 3.84, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.64 (1H, dd, H-2'), 5.48, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.26 (1H, t, Ar-H), 7.35 (2H, t, Ar-H), 7.42 (2H, d, Ar-H), 8.38 (1H, s, H-8), 9.49 (1H, s, N-H). HPLC retention time 22.19 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 100% purity at 250 nm).

EXAMPLE 6

2,5'-Dichloro-5'-deoxy-*N*-(3-phenylthio-1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(4-phenylthio-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (0.5 g, 1 mmol) was subjected to the reaction conditions described above, providing the title 2,5'-dichloro-5'-deoxy-*N*-(3-phenylthio-1-piperidinyl)adenosine (mixture of diastereoisomers) as a foam (0.48 g, 94%) following flash chromatography on silica gel. ^{1}H-NMR (400MHz, DMSO-d_6) δ 3.84, 3.92 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.64 (1H, dd, H--2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.22 (1H, t, Ar-H), 7.31 (2H, t, Ar-H), 7.43 (2H, d, Ar-H), 8.39 (1H, s, H-8). HPLC retention time 17.08 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 98.7% purity at 250 nm).

EXAMPLE 7

2,5'-Dichloro-5'-deoxy-*N*-(4-phenylsulphinyl-1-piperidinyl)adenosine

2',3'-Di-*O*-acetyl-2,5'-dichloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)-adenosine (prepared by acetylation of Example 5) (2.95 g, 5 mmol) was dissolved in dry dichloromethane (100 ml). "Oxone" (7.7 g, 2.5 equiv.) and wet clay (Hirano, M., Tomaru, J. and Morimoto, T. Bull. Chem. Soc. Japan, **1991**, *64*, 3752-3754) (5.95 g) were introduced with vigourous stirring. Both the phenylsulphinyl product (R_f = 0.21) and the phenylsulphonyl product (R_f = 0.45) were apparent by TLC [SiO_2, ethyl acetate/methanol (9:1)] and after 0.5 h. reaction time the reaction mixture was filtered. The filtrate was washed with water (2 x 100 ml), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1), then with ethyl acetate, and finally with a mixture of ethyl acetate and methanol (19:1), to provide 2',3'-di-*O*-acetyl-2,5'-dichloro-5'-deoxy-*N*-(4-phenylsulphinyl-1-piperidinyl)adenosine (0.18 g, 6%) and 2',3'-di-*O*-

acetyl-2,5'-dichloro-5'-deoxy-*N*-(4phenylsulphonyl-1-piperidinyl)-adenosine (1.2 g, 39 %) as foams.

5'-Deoxy-2,5'-dichloro-*N*-(4-phenylsulphinyl-1-piperidinyl)adenosine

2',3-Di-*O*-acetyl-2,5'-dichloro-5'-deoxy-*N*-(4-phenylsulphinyl-1-piperidinyl)adenosine (0.22 g, 0.36 mmol) was dissolved in methanol (10 ml) and methanolic ammonia (1 ml) was introduced. After 1 h. at room temperature, the reaction mixture was evaporated to a residue and purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and ethanol (9:1) to provide 2,5'-dichloro-5'-deoxy-*N*-(4-phenylsulphinyl-1-piperidinyl)adenosine (0.1 g, 53%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) δ 3.84, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.63 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.53 - 7.66 (5H, m, Ar-H), 8.38 (1H, s, H-8). HPLC retention time 14.24 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 95.4% purity at 250 nm).

EXAMPLE 8

2,5'-Dichloro-5'-deoxy-*N*-(4-phenylsulphonyl-1-piperidinyl)adenosine

2',3-Di-*O*-acetyl-2,5'-dichloro-5'-deoxy*N*-(4-phenylsulphonyl-1-piperidinyl)adenosine (generated during the preparation of Example 7) (1.2 g, 1.9 mmol) was dissolved in methanol (90ml) and methanolic ammonia (10 ml) was introduced. After 0.5 h. at room temperature, the reaction mixture was evaporated to a residue and purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and ethanol (9:1) to provide 2,5'-dichloro-5'-deoxy-*N*-(4-phenylsulphonyl-1-piperidinyl)adenosine (0.82 g, 79%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) δ

3.84, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, dt, H-4'), 4.16 (1H, ps t, H-3'), 4.62 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.71 (2H, t, Ar-H), 7.80 (1H, t, Ar-H), 7.90 (1H, d, Ar-H), 8.39 (1H, s, H-8). HPLC retention time 13.78 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.9% purity at 250 nm).

EXAMPLE 9

2,5'-Dichloro-5'-deoxy-*N*-(4-phenyl-1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(4-phenyl-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (0.3 g, 0.65 mmol) was subjected to the chlorination conditions described above, providing the title 2,5'-dichloro-5'-deoxy-*N*-(4phenyl-1-piperidinyl)adenosine as a foam (0.28 g, 90%), ^{1}H-NMR (400MHz, DMSO-d$_6$) δ 3.86, 3.95 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.11 (1H, q, H-4'), 4.21 (1H, q, H-3'), 4.66 (1H, dd, H-2'), 5.49, 5.63 (2H, 2d, 2'- and 3'-OH), 5.89 (1H, d, H-1'), 7.20 (1H, dt, Ph-C-H), 7.31 (5H, d, Ar-H), 8.40 (1H, s, H-8), 9.45 (1H, s, N-H). HPLC retention time 20.92 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99.75% purity at 250 nm).

EXAMPLE 10

2,5'-Dichloro-5'-deoxy-*N*-(1-morpholinyl)adenosine

This compound was prepared by the method described in Example 2. 2-Chloro-*N*-(1-morpholinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (1.0 g, 2.6 mmol) was subjected to the chlorination conditions described above, providing the title 2,5'-dichloro-5'-deoxy-*N*-(1-morpholinyl)-

adenosine as a foam (0.78 g, 74%), ^{1}H-NMR (400MHz, DMSO-d_6) δ 2.38 (4H, br, morpholine C-H), 3.71 (4H, br, morpholine C-H), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.64 (1H, q, H-2'), 5.50, 5.63 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.41 (1H, s, H-8), 9.50 (1H, s, NH). HPLC retention time 7.82 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 97.8% purity at 250 nm).

$C_{14}H_{18}Cl_2N_6O_4$.0.5 EtOH requires C, 42.1; H, 4.9; N, 19.6. Found: C, 41.6; H, 5.2; N, 19.0%.

EXAMPLE 11

2,5'-Dichloro-5'-deoxy-*N*-(dimethylamino)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(dimethylamino)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.62 g, 1.8 mmol) was subjected to the chlorination conditions described above, providing the title 2,5'-dichloro-5'-deoxy-*N*-(dimethylamino)adenosine as a solid (0.23 g, 41%) after column chromatography, m.p. 188-189°C, ^{1}H-NMR (400MHz, DMSO-d_6) δ 2.59 (6H, s, N(CH_3)$_2$), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.66 (1H, q, H-2'), 5.50, 5.62 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.39 (1H, br, NH).

$C_{12}H_{16}Cl_2N_6O_3$.0.25 H_2O. 0.25 EtOH requires C, 39.6; H, 4.8; N, 22.2. Found: C, 39.5; H, 4.5; N, 22.3%.

EXAMPLE 12

2,5'-Dichloro-5'-deoxy-*N*-methoxyadenosine

This compound was prepared by the method described in Example 2. 2-Chloro-*N*-(methoxy)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.8 g, 2.4 mmol) was subjected to the chlorination conditions described above, providing the title 2,5'-dichloro-5'-deoxy-*N*-methoxyadenosine as a foam (0.34 g, 40%), ^{1}H-NMR (400MHz, DMSO-d_6) δ 3.78 (3H, s, -OCH_3), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.19 (1H, q, H-3'), 4.66 (1H, q, H-2'), 5.51, 5.65 (1H, 2d, 2'-and 3'-OH), 5.90 (1H, d, H-1'), 8.45 (1H, s, H-8), 11.59 (1H, s, NH). HPLC retention time 6.99 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.5% purity at 250 nm).

EXAMPLE 13

N-Cyclopentoxy-2,5'-dichloro-5'-deoxy-adenosine

This compound was prepared by general method C, described in more detail in Example 2. *N*-Cyclopentoxy-2-chloroadenosine [WO 93/23417 (Novo Nordisk A/S)] (1.0 g, 2.6 mmol) was subjected to the chlorination conditions described above, providing the title *N*-cyclopentoxy-2,5'-dichloro-5'-deoxy-adenosine as a foam (0.82 g, 78%), ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.49 - 1.92 (8H, 3m, cyclopentyl C-H), 3.86, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.11 (1H, q, H-4'), 4.20 (1H, q, H-3'), 4.59 (1H, m, -OC-H), 4.67 (1H, q, H-2'), 5.51, 5.64 (1H, 2d, 2'-and 3'-OH), 5.90 (1H, d, H-1'), 8.44 (1H, s, H-8), 11.44 (1H, s, NH). HPLC retention time 12.2 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 97.4% purity at 250 nm).

$C_{15}H_{19}Cl_2N_5O_4$.0.5 EtOH requires C, 45.0; H, 5.2; N, 16.4. Found: C, 45.2; H, 5.1; N, 16.2%.

EXAMPLE 14

2-Bromo-5'-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Bromo-*N*-(1-piperidinyl)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.06 g, 0.14 mmol) was subjected to the chlorination conditions described above, providing the title 2-bromo-5'-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine as a foam (0.016 g, 26%), ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.37 (2H, br, piperidine C-H), 1.64 (4H, br, piperidine C-H), 2.80 (4H, br, piperidine C-H), 3.85, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.65 (1H, q, H-2'), 5.48, 5.62 (1H, 2d, 2'-and 3'-OH), 5.87 (1H, d, H-1'), 8.33 (1H, s, H-8), 9.36 (1H, s, NH). HPLC retention time 9.65 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 94% purity at 250 nm).

EXAMPLE 15

2-Amino-5'-chloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Amino-*N*-(4-phenylthio-1-piperidinyl)adenosine [prepared by reaction of 9-(2,3,5-tri-*O*-acetyl-ß-D-ribofuranosyl)-9H-2-amino-6-chloro-9H-purine (Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) with 1-amino-4-phenylthiopiperidine] (0.47 g, 1.0 mmol) was subjected to the chlorination conditions described above. Column

chromatography on silica gel, eluting initially with a mixture of heptane and ethyl acetate (7:3), increasing polarity to pure ethyl acetate provided the title 2-amino-5'-chloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)-adenosine (0.1 g, 20%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.65 (2H, dq, piperidine C-H), 1.91 - 2.01 (2H, br, piperidine C-H), 2.75 (2H, br t, piperidine C-H), 2.98 - 3.07 (2H, br, piperidine C-H), 3.82, 3.92 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.04 (1H, dt, H-4'), 4.15 (1H, q, H-3'), 4.64 (1H, dd, H-2'), 5.36, 5.52 (2H, 2d, 2'- and 3'-OH), 5.77 (1H, d, H-1'), 5.96 (1H, br s, -NH_2), 7.27 (1H, t, Ar-H), 7.37 (2H, t, Ar-H), 7.42 (2H, d, Ar-H), 7.91, 8.18 (2H, 2s, H-8, N-H).

EXAMPLE 16

5'-Chloro-5'-deoxy-2-methylthio-*N*-(1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Methylthio-*N*-(1-piperidinyl)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.15 g, 0.38 mmol) was subjected to the chlorination conditions described above, providing 5'-chloro-5'-deoxy-2-methylthio-*N*-(1-piperidinyl)adenosine as a solid (0.07 g, 45%) mp 213 - 215°C. ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.37 (2H, br, piperidine C-H), 1.62 (4H, br q, piperidine C-H), 2.48 (3H, s, -SCH_3), 2.81 (4H, br, piperidine C-H), 3.83, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.08 (1H, q, H-4'), 4.23 (1H, q, H-3'), 4.75 (1H, q, H-2'), 5.47, 5.59 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.22 (1H, s, H-8), 8.85 (1H, s, NH). HPLC retention time 9.15 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.4% purity at 250 nm).

EXAMPLE 17

5'-Bromo-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (3.08 g, 8 mmol) was subjected to the same reaction conditions described above, except that thionyl bromide was substituted for thionyl chloride. The procedure provided the desired 5'-bromo-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine as a foam (0.19 g, 9%) after column chromatography, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.37 (2H, br, piperidine C-H), 1.62 (4H, m, piperidine C-H), 2.80 (4H, br, piperidine C-H), 3.72, 3.82 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, dt, H-4'), 4.17 (1H, dt, H-3'), 4.68 (1H, q, H-2'), 5.50, 5.62 (1H, 2d, 2'- and 3'-OH), 5.88 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.36 (1H, br, NH). HPLC retention time 11.06 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.4% purity at 250 nm).

$C_{15}H_{20}N_6BrClO_3.1.3\ H_2O$ requires C, 38.2; H, 4.8; N, 17.8. Found: C, 38.7; H, 4.7; N, 17.3%.

EXAMPLE 18

2-Chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine

This compound was prepared using general method A starting from 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose prepared according to general method B.

Methyl 5-Deoxy-5-fluoro 2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside

Methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(p-toluenesulfonyl)-ß-ribofuranoside (28.7 g, 80 mmol) was dissolved in dry acetonitrile (100 ml). Tetra-n-butylammonium fluoride (100 ml, 1.0M in THF) was added dropwise and the reaction mixture was heated at 80°C for 72 h. After cooling to room temperature, the mixture was diluted with dichloromethane (200 ml), washed with water (3 x 50 ml) and dried ($MgSO_4$). Evaporation provided a residue which was purified by flash chromatography eluting with a mixture of ethyl acetate and n-heptane (1:3) to give methyl 5-deoxy-5-fluoro-2,3-*O*-(1-methylethylidene)--ß-D-ribofuranoside (13.6 g, 82%) as a clear oil, ^1H NMR ($CDCl_3$)δ 1.34 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.35 (3H, s, $-OCH_3$), 4.29 - 4.48 (3H, m, H-4, H-5_a and H-5_b), 4.60 (1H, d, H-3), 4.70 (1H, d, H-2), 4.99 (1H, d, H-1).

1,2,3-Tri-*O*-acetyl-5-deoxy-5-fluoro-ß-D-ribofuranose

Methyl 5-deoxy-5-fluoro-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside (5.0 g, 24 mmol) was treated with sulfuric acid (0.02M, 40 ml) and heated at reflux for 4 h. The reaction mixture was cooled, neutralized with barium carbonate to pH 7, filtered and evaporated to an oil. The oil was dried by coevaporation with ethanol, and the residue was dissolved in dichloromethane (50 ml). Acetic anhydride (25 ml) and pyridine (25 ml) were introduced, and the reaction mixture was stirred for 16 h before being poured onto ice (100 ml). The cool suspension was extracted with dichloromethane (3 x 100 ml), and the combined extracts was washed with 2N hydrochloric acid solution (50 ml) and aqueous sodium bicarbonate solution (50 ml). The organic phase was dried ($MgSO_4$), evaporated in vacuo and the residue was purified by flash chromatography, eluting with a mixture of dichloromethane and 10% ammonia in ethanol (97:3) to provide 1,2,3-tri-*O*-acetyl-5-deoxy-5--fluoro-ß-D-ribofuranose (5.3 g, 79%), which crystallized on standing.

Recrystallisation from absolute ethanol provided analytically pure material, m.p. 98 - 101°C, ^{1}H NMR ($CDCl_3$) δ 2.09 (3H, s, -$OCOCH_3$), 2.10 (3H, s, -$OCOCH_3$), 2.14 (3H, s, -$OCOCH_3$), 4.34 (1H, ddd, H-4), 4.49 (1H, ddd, H-5_a), 4.52 (1H, ddd, H-5_b), 5.36 (1H, d, H-3), 5.46 (1H, dd, H-2), 6.17 (1H, s, H-1).

$C_{11}H_{15}FO_7$ requires C, 47.5; H 5.4. Found: C, 47.7; H, 5.6%.

9-[(2',3'-Di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl)]-2,6-dichloro-9H-purine

A mixture of the above 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose (5.0 g, 18 mmol) and 2,6-dichloropurine (3.4 g, 18 mmol) was heated to 160°C. A catalytic amount of sulfuric acid (one drop) was added at which point a homogeneuos melt was obtained. The fusion was continued at 160°C under oil pump vacuum for 0.5 h. After cooling, the reaction mixture was dissolved in chloroform (200 ml) and washed with aqueous sodium bicarbonate (3 x 50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and evaporated in vacuo before purification by flash chromatography. Elution with a mixture of dichloromethane and 10% ammonia in ethanol (98:2) afforded an anomeric mixture of 9[(2',3'-di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl)]-2,6-dichloro-9H-purine (4.5 g, 90%) as a gum, ^{1}H NMR (DMSO-d_6)δ (α-anomer) 1.84 (3H, s, -$OCOCH_3$), 2.00 (3H, s, -$OCOCH_3$), 4.71 (2H, dd, H-5'a, H-5'b), 5.98 (1H, ddd, H-4'), 5.48 (1H, t, H-3), 5.68 (1H, t, H-2'), 6.73 (1H, d, H-1'), 8.92 (1H, s, H-8); (ß-anomer) 2.05 (3H, s, -$OCOCH_3$), 2.11 (3H, s, -$COCH_3$), 4.50 (1H, ddd, H-4), 4.77 (2H, dd, H-$5'_a$ and H-5_b'), 5.61 (1H, t, H-3), 5.89 (1H, t, H-2'), 6.33 (1H, d, H-1), 8.92 (1H, s, H-8).

2',3'-Di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine:

An *α*/*β* mixture of 9-[(2',3'-di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl])-2,6-dichloro-9H-purine (1.24 g, 3.0 mmol), *N*,*N*-diisopropylethyl amine (0.79 g, 6.1 mmol) and 1-aminopiperidine (0.60 g, 6.0 mmol) were stirred in dioxan (20 ml) for 4 h. The reaction mixture was diluted with dichloromethane (200 ml) and washed with water (2 x 50 ml). After drying over ($MgSO_4$) the organic phase was evaporated in vacuo and the residue was purified by flash chromatography. Elution with dichloromethane and 10% ammonia in ethanol (98:2) afforded the *β*-anomer of 2',3'-di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine (0.40 g, 28%) as a foam. HPLC retention time 14.8 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

The above 2',3'-di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)-adenosine (0.38 g, 0.8 mmol) was dissolved in methanolic ammonia (15 ml) and stirred for 1 h. The reaction mixture was evaporated in vacuo and the resultant residue was purified by flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (95:5) to afford 2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine (1.8 g, 86%) as a white solid, m.p. 199-201°C. ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.35 (2H, br, piperidine C-H), 1.52 (4H, br, piperidine C-H), 2.80 (4H, br, piperidine C-H), 4.10 (1H, ddd, H-4'), 4.20 (1H, br, H-3'), 4.51 (1H, br, H-2'), 4.65 (2H, dd, H-5'$_a$ and H-5'$_b$), 5.88 (1H, d, H-1'), 8.28 (1H, s, H-8). HPLC retention time 7.15 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

$C_{15}H_{20}ClFN_6O_3$, $0.75H_2O$ requires C, 45.2; H, 5.4; N, 21.1. Found: C, 45.2; H, 5.2; N, 20.8%.

EXAMPLE 19

2-Chloro-5'-deoxy-5'-fluoro-*N*-benzyloxyadenosine

This compound was prepared by general method A, described in more detail in Example 18 by reacting *O*-benzylhydroxylamine hydrochloride (0.80 g, 5.0 mmol) with 9-[(2',3'-di-*O*-acetyl-5'deoxy-5'-fluoro-D-ribofuranosyl)]-2,6-dichloro-9H-purine (1.0 g, 2.5 mmol) as described above. The product was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (98:2) giving the intermediate 2',3'-di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-benzyloxyadenosine (0.2 g, 16%). Deacetylation was performed in methanolic ammonia to afford 2-chloro-5'-deoxy-5'-fluoro-*N*-benzyloxyadenosine as a foam (0.11 g, 89%) after flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (95:5). ^{1}H-NMR (400MHz, DMSO-d_6) δ 4.12 (1H, m, H-4'), 4.20 (1H, m, H-3'), 4.53 (1H, m, H-2'), 4.65 (2H, dd, H-5'$_a$ and H-5'$_b$), 5.00 (2H, s, -CH_2-), 5.48, 5.60 (2H, 2d, 2'-and 3'-OH) 5.91 (1H, d, H-1'), 7.30 -7.55 (5H, m, Ar-H), 8.43 (1H, s, H-8), 11.65 (1H, s, N-H). HPLC retention time 14.60 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96% purity at 250 nm).

EXAMPLE 20

(S)-2-Chloro-5'-*O*-methyl-*N*-(2-(methylmethoxy)-1-pyrrolidinyl)adenosine

The title compound was prepared using general method A starting from 5-*O*-methyl-1,2,3-tri-*O*-acetyl-D-ribofuranose, itself prepared according to general method B.

Methyl 5-*O*-methyl-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside.

Methyl 2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside (13.3 g, 60 mmol), 2,6-di-t-butyl-4-methylpyridine (20.0 g, 100 mmol) and methyl trifluoromethylsulfonate (16.0 g, 100 mmol) were dissolved in dry dichloromethane (150 ml) placed in a closed reactor and heated to 80°C. After cooling, the reaction mixture was poured onto ice (150 ml). After standing, the product was extracted into dichloromethane (2 x 100 ml) and the combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography eluting with a mixture of cyclohexane and ethyl acetate (3:1) to afford methyl 5-*O*-methyl-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside (8.0 g, 61%) as an oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.30 (3H, s, $-CH_3$), 1.50 (3H, s, $-CH_3$), 3.32 (3H, s, $-OCH_3$), 3.39 (3H, s, $-OCH_3$), 3.35 - 3.45 (2H, m, H-5_a and H-5_b), 4.30 (1H, t, H-4), 4.57 (1H, d, H-3), 4.65 (1H, d, H-2), 4.97 (1H, s, H-1).

1,2,3-Tri-*O*-acetyl-5-*O*-methyl-ß-D-ribofuranose.

5-*O*-Methyl-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside (3.0 g, 14 mmol) was dissolved in a mixture of sulfuric acid (0.02M, 100 ml) and ethanol (50 ml) and heated at 80°C for 6 h and stirred for 20 h at 20°C. The reaction mixture was neutralised with aqueous sodium bicarbonate and concentrated in vacuo. The residual oil was dried and acetylated in a mixture of dichloromethane (100 ml), acetic anhydride (8.5 g, 83 mmol) and triethylamine (16.7 g, 165 mmol) at 20°C for 20 h. The reaction mixture was washed with hydrochloric acid (1M, 50 ml) and water (50 ml). The organic phase was dried ($MgSO_4$) and concentrated to an oil before being purified by flash chromatography. Elution with a mixture of cyclohexane and ethyl acetate (6:4) provided 1,2,3-tri-*O*-acetyl-5-*O*-methyl-ß-D-ribofuranose (2.5g, 62%) as an oil.

9-(2',3'-Di-*O*-acetyl-5'-*O*-methyl-ß-D-ribofuranosyl)-2,6-dichloro-9H-

purine

5-*O*-Methyl-1,2,3-tri-*O*-acetyl-D-ribofuranose (5.0 g, 17 mmol) and 2,6-dichloropurine (3.3 g, 17 mmol) were thoroughly mixed. A catalytic amount of p-toluene sulfuric acid (50 mg) was added and the reaction mixture was heated to 140°C at which point a homogeneous melt was obtained. The fusion was continued at 140°C under oil pump vacuum for 0.5 h. The reaction mixture was dissolved in chloroform (200 ml) and washed with aqueous sodium bicarbonate (3 x 50 ml) and water (2 x 50 ml). The organic phase was dried ($MgSO_4$), evaporated in vacuo and purified by flash chromatography eluting with a mixture of n-heptane and ethyl acetate (1:1) to provide 9-(2',3'-di-*O*-acetyl-5'-*O*-methyl-ß-D--ribofuranosyl)-2,6-dichloro-9H-purine (1.0 g, 14%) as an oil which crystallized from diethyl ether. A mixture of *α*/ß-anomers (1.2 g, 17%) was also isolated, with mp 59 - 61°C. ^{1}H-NMR (400MHz,$CDCL_3$) δ 2.06 (3H, s, -$OCOCH_3$), 3.49 (3H, s, OCH_3), 3.67, 3.72 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.39 (1H, d, H-4'), 5.58 (1H, d, H-3'), 5.75 (1H, t, H-2'), 6.38 (1H, d, H-1'), 8.56 (1H, s, H-8).

$C_{15}H_{16}Cl_2N_4O_6$ requires C, 43.0; H, 3.9; N, 13.4. Found C, 43.1, H, 3.9, N, 13.2%.

(S)-2',3'-Di-*O*-acetyl-2-chloro-5'-*O*-methyl-*N*-[2-(methylmethoxy)-1-pyrro-lidinyl]adenosine.

9-(2',3'-Di-*O*-acetyl-5'-*O*-methyl-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.3 g, 3.1 mmol), (S)-*N*-amino-2-(methoxymethyl)pyrrolidine (0.81 g, 6.2 mmol) and triethylamine (0.63 g, 6.2 mmol) were dissolved in dioxan. After stirring for 20 h the reaction mixture was diluted with dichloromethane (150 ml) and washed with water (2 x 75 ml). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The

resultant residue was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (97:3) to afford (S)-2',3'-di-*O*-acetyl-2-chloro-5'-*O*-methyl-*N*-[2-(methyl-methoxy)-1-pyrrolidinyl]adenosine (0.28 g, 18%) as a foam. ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.70 - 2.10 (4H, m, pyrrolidine C-H), 2.05 (3H, s, -$OCOCH_3$), 2.18 (3H, s, -$OCOCH_3$), 2.85 (1H, m, pyrrolidine C-H), 3.10 (1H, br, pyrrolidine C-H), 3.22 (3H, s, -OCH_3), 3.35 - 3.70 (8H, m, H-5'$_a$ and H-5'$_b$, -OCH_3, pyrrolidine, -CH_2-), 4.32 (1H, s, H-4'), 5.55 (1H, d, H-3'), 5.75 (1H, t, H-3'), 6.32 (1H, d, H-1'), 8.17 (1H, s, H-8). HPLC retention time 15.57 min. (gradient elution over 25 min.; 20-80% acetonitrile/0.1% TFA in water).

The above (S)-2',3'-di-*O*-acetyl-2-chloro-5'-*O*-methyl-*N*-[2-(methyl-methoxy)-1-pyrrolidinyl]adenosine (0.26 g, 0.52 mmol) was treated with methanolic ammonia for 1.5 h at room temperature. The crude product was purified by flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (9:1) to give (S)2-chloro-5'-*O*-methyl-*N*-(2-(methylmethoxy)-1-pyrrolidinyl)adenosine (0.16 g, 72%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.55 (1H, m, pyrrolidine C-H), 1.75 (2H, m, pyrrolidine C-H), 1.97 (1H, m, pyrrolidine C-H), 3.51, 3.59 (1H, ABX, H-5'$_a$ and H-5'$_b$), 4.02 (1H, dd, H-4'), 4.10 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.82 (1H, d, H-1'), 8.32 (1H, s, H-8). HPLC retention time 7.67 min. (gradient elution over 25 min.; 20-80% acetonitrile/0.1% TFA in water).

$C_{17}H_{25}ClN_6O_5 \cdot 0.5H_2O$ requires C, 46.3; H, 5.8; N, 18.5. Found C, 46.7; H, 6.1; N, 18.6%.

EXAMPLE 21

2-Chloro-5'-deoxy-5'-methylthio-*N*-(1-piperidinyl)adenosine

The title compound was prepared according to general method C.

2-Chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl) adenosine tosylate salt

2-Chloro-*N*-(1-piperidinyl)adenosine (1.5 g, 3.9 mmol), 2,2-dimethoxypropane (0.9 g, 8.6 mmol) and 4-toluenesulfonic acid monohydrate (1.6 g, 18.6 mmol) was stirred in acetone (25 ml) for 72 h. Further 2,2-dimethoxypropane (0.9 g, 8.6 mmol) was added. After a further 24 h the tosylate salt of 2-chloro-2',3'-*O*-(1- methylethylidene)-*N*-(1-piperidinyl)adenosine (1.78 g, 76%) was collected by filtration, m.p. 169-170°C, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.35 (3H, s, -CH_3), 1.46 (2H, br, piperidine C-H), 1.55 (3H, s, -CH_3), 1.75 (4H, m, piperidine -CH), 3.10 (4H, br, piperidine C-H), 3.55 (2H, ABX, H-5$_a$' and H-5'$_b$), 4.29 (1H, m, H-4'), 4.95 (1H, dd, H-3'), 5.30 (1H, dd, H-2'), 6.15 (1H, d, H-1'), 8.72 (1H, s, H-8). HPLC retention time 14.87 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

$C_{25}H_{33}ClN_6O_7S$ requires C, 50.3; H, 5.6; N, 14.1. Found C, 50.7; H, 5.8; N, 13.7%.

2-Chloro-5'-deoxy-5'-methylthio-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine

2-Chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl) adenosine tosylate (0.5 g, 0.84 mmol), tributylphosphine (1.7 g, 8.4 mmol) and dimethyldisulfide (0.4 g, 4.20 mmol) were stirred in dry dimethylformamide (5 ml) under nitrogen for 7 days. The reaction mixture was poured into ice (50 ml) and after standing for 1 h was extracted with dichloromethane (3 x 25 ml). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography eluting

with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to give 2-chloro-5'-deoxy-5'-methylthio-2',3'-*O*-(1-methylethylidene)-*N*--(1-piperidinyl)adenosine (0.12 g, 31%) as a foam. ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.40 (3H, s, $-CH_3$), 1.45 (2H, m, piperidine C-H), 1.65 (3H, s, $-CH_3$), 1.70 - 1.85 (4H, m, piperidine C-H), 2.15 (3H, s, $-SCH_3$), 2.85 (4H, m, piperidine C-H), 4.02, 4.38 (2H, ABX, H-5'$_a$ and H-5'$_b$), 5.05 (1H, dd, H-4'), 5.38 (1H, dd, H-3'), 6.05 (1H, d, H-2'), 6.50 (1H, br, H-1'), 7.83 (1H, s, H-8).

2-Chloro-5'-deoxy-5'-methylthio-*N*-(1-piperidinyl)adenosine

2-Chloro-5'-deoxy-5'-methylthio-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine (0.10 g, 0.22 mmol) was reacted in a mixture of water (2.5 ml) and ethanol (2.5 ml) containing sulfuric acid (0.1 ml) for 10 h at 60°C. The reaction mixture was diluted with dichloromethane (100 ml) and washed with aqueous sodium bicarbonate (2 x 25 ml) followed by water (25 ml). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to provide 2-chloro-5'deoxy-5'-methylthio-*N*-(1-piperidinyl)adenosine (0.75 g, 82%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.39 (2H, br, piperidine C-H), 1.62 (4H, m, piperidine C-H), 2.05 (3H, s, $-SCH_3$), 2.75 - 2.80 (8H, m, H-5'$_a$, H-5'$_b$, piperidine C-H), 4.01 (1H, m, H-4'), 4.10 (1H, m, H-3'), 4.65 (1H, br, H-2'), 6.82 (1H, d, H-1'), 8.39 (1H, s, H-8). HPLC retention time 9.90 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, purity 96% at 250 nm).

EXAMPLE 22

2-Chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine

The title compound was prepared using general method A starting from 1,2,3-tri-*O*-acetyl-5-deoxy-5-cyano-D-ribofuranose prepared according to general method B as follows:

Methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzenesulfonyl)-ß-D-ribofuranoside

Methyl 2,3-*O*-(1-methylethylidene)-ß-D-ribofuranose (37 g, 180 mmol) and triethylamine (54.6 g, 540 mmol) were dissolved in dry dichloromethane (100 ml). 4-Nitrobenzenesulfonyl chloride (40.0 g, 180 mmol) was added dropwise at 0°C over 0.5 h. After stirring for 20 h, the reaction mixture was diluted with dichloromethane (1000 ml) and washed with aqueous ammonium chloride (2 x 250 ml) and water (250 ml). After drying ($MgSO_4$) the organic phase was evaporated to dryness in vacuo. Recrystallization from ethyl acetate gave methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzenesulfonyl)-ß-D-ribofuranoside as a white solid (54.8 g, 85%), m.p. 97-98°C, ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.38 (3H, s, $-CH_3$), 1.45 (3H, s, $-CH_3$), 3.26 (3H, s, $-OCH_3$), 4.13 (2H, ABX, H-5_a and H-5_b), 4.32 (1H, t, H-4), 4.53 (1H, d, H-3), 4.61 (1H, d, H-2), 4.95 (1H, s, H-1), 8.12 (2H, d, Ar-H), 8.40 (2H, d, Ar-H).

Methyl 5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside.

Methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzenesulfonyl)-ß-D-ribofuranoside (45.3 g, 120 m mol) was added over 1.5 h to a suspension of sodium cyanide (6.8 g, 140 mmol) in dry dimethylformamide (1000 ml). The reaction mixture was heated to 50°C for 3 h before being poured onto ice (500 ml). This mixture was extracted with dichloromethane (3 x 500 ml), the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled under vacuum to give methyl 5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside as an oil (6.3 g,

25%), bp 110-115°C/0.6 mm Hg. ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.30 (3H, s, $-CH_3$), 1.48 (3H, s, $-CH_3$), 2.62, 2.70 (2H, ABX, H-5_a and H-5_b), 3.40 (3H, s, $-OCH_3$), 4.45 (1H, s, H-4), 4.61 (1H, d, H-3), 4.63 (1H, d, H-2), 5.00 (1H, s, H-1).

Methyl 2,3-di-*O*-benzoyl-5-cyano-5-deoxy-ß-D-ribofuranoside

Methyl 5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)-ß-D-ribofuranoside (18.7 g, 87 mmol) and Amberlyst (H^+ form, 84 g) were mixed and heated at reflux for 24 h. The reaction mixture was filtered and evaporated to a residue which was dissolved in dichloromethane (200 ml), which was washed with water (300 ml). The separated water phase was extracted with ethyl acetate (7 x 200 ml), combined with the earlier organic phase and dried ($MgSO_4$). Evaporation provided the intermediate methyl 5-cyano-5-deoxy-ß-D-ribofuranoside (6.85 g) which was dissolved in dichloromethane (200 ml). Benzoyl chloride (24 g, 170 mmol) and triethlamine (34 g, 340 mmol) were introduced and the reaction mixture was stirred for 20 h. at ambient temperature before being washed with 1 N hydrochloric acid solution (2 x 85 ml) and saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to a residue which was purified by flash chromatography on silica gel. Elution with a mixture of heptane and ethyl acetate (3:1), increasing polarity to a 9:1 mixture of these solvents provided methyl 2,3-*O*-dibenzoyl-5-cyano-5-deoxy-ß-D-ribofuranoside (13.01 g, 40%), ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.04, 3.20 (2H, ABX, H-5_a and H-5_b), 3.43 (3H, s, $-OCH_3$), 4.67 (1H, d, H-4), 5.25 (1H, s, H-1), 5.50 - 5.57 (2H, m, H-3 and H-4), 7.4 - 7.95 (10H, 6m, Ar-H).

1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-cyano-5-deoxy-D-ribofuranose

Acetic acid (74.5 ml, 1.3 mol), acetic anhydride (173.8 ml, 1840 mmol)

and sulphuric acid (1.7 ml, 32 mmol) were mixed together and methyl 2,3-*O*-dibenzoyl-5-cyano-5-deoxy-ß-D-ribofuranoside (13.01 g, 35 mmol) was added. The reaction mixture was stirred for 20 h at ambient temperature before sodium acetate (37 g, 450 mmol) was introduced. After 30 min. stirring the reaction mixture was filtered, the filter pad was washed with ethyl acetate (100 ml) and the filtrate was evaporated to a residue which was coevaporated with toluene (250 ml). The residue was dissolved in a mixture of ethyl acetate (250 ml) and water (250 ml). The ethyl acetate phase was washed with water (2 x 100 ml) and saturated brine (50 ml) before being dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel. Elution with a mixture of hexane and ethyl acetate (9:1), increasing polarity to a 4:1 mixture of these solvents provided the title 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-cyano-5-deoxy-D-ribofuranose as a solid single isomer (2.85 g, 20%), mp 124-126°C, ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.22 (3H, s, $-OCOCH_3$), 2.92, 3.02 (2H, ABX, H-5_a and H-5_b), 4.61 (1H, dt, H-4), 5.70 - 5.80 (2H, 2m, H-2 and H-3), 6.38 (1H, s, H-1) and a mixture of isomers as a gum (7.5 g, 52%).

9-(2',3'-Di-*O*-benzoyl-5'-cyano-5'-deoxy-D-ribofuranosyl)-2,6-dichloro-9H-purine

A mixture of 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-cyano-5-deoxy-D-ribofuranose (2.8 g, 6.8 mmol) and 2,6-dichloro-9H-purine (1.36 g, 7.2 mmol) were heated at 145°C for 1.25 h in the presence of a catalytic amount of p-toluenesulphonic acid (0.025 g). The reaction mixture was dissolved in ethyl acetate (100 ml) and washed with aqueous sodium bicarbonate (100 ml) followed by saturated brine (100 ml). The organic phase was dried ($MgSO_4$), and the solid residue was recrystallised from 2-propanol to provide 9-(2',3'-di-*O*-benzoyl-5'-cyano-5'-deoxy-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (3.3 g, 90%), m.p.

143-145°C, ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.15, 3.25 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.74 (1H, dt, H-4'), 5.95 (1H, t, H-3'), 6.12 (1H, t, H-2'), 6.42 (1H, d, H-1'), 7.36 - 8.05 (10H, 4m, Ar-H), 8.40 (1H, s, H-8).

2',3'-Di-*O*-benzoyl-2-chloro-5'cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine

9-(2',3'-di-*O*-benzoyl-5'-cyano-5'-deoxy-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.75 g, 3.25 mmol), triethylamine (0.9 ml, 6.5 mmol) and 1-aminopiperidine (0.7 ml, 6.5 mmol) were stirred in dioxan (20 ml) for 2 h. The reaction mixture was evaporated and the residue dissolved in dichloromethane (10 ml) and purified by flash chromatography eluting with a mixture of heptane and ethyl acetate (4:1), increasing polarity to a 1:1 mixture of these solvents provided 2',3'-di-*O*-benzyl-2-chloro-5'-cyano-5'deoxy-*N*-(1-piperidinyl)adenosine (1.19 g, 61%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 3.15, 3.31 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.68 (1H, dd, H-4'), 5.99 (1H, t, H-3'), 6.11 (H, t , H-2'), 6.36 (1H, d, H-1'), 7.36 - 8.00 (10H, m, Ar-H), 8.03 (1H, s, H-8). HPLC retention time 17.26 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

2-Chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine

2',3'-*O*-Benzoyl-2-chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine (1.5 g, 2.5 mmol) was dissolved in methanolic ammonia (30 ml) and stirred at ambient temperature for 3 h. Following evaporation, the crude product was purified by flash chromatography eluting with a mixture of heptane and ethyl acetate, followed by ethyl acetate alone to provide 2-chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine as a solid (0.6 g, 61%). Recrystallization from ethyl acetate provided an analytical sample (0.36 g, 37%), m.p. 192-193°C, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.38 (2H, br, piperidine C-H), 1.63 (4H, q, piperidine C-H), 2.81 (4H, br,

piperidine C-H), 3.05 (2H, d, H-5'$_a$ and H-5'$_b$), 4.12 (2H, m, H-4'and H-3'), 4.65 (1H, m, H-2'), 5.53, 5.67 (2H, 2d, 2'-and 3'-OH), 5.87 (1H, d, H-1'), 8.37 (1H, s, H-8). HPLC retention time 11.9 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 100% at 250 nm).

$C_{16}H_{20}ClN_7O_3$ requires C, 48.8; H, 5.1; N, 24.9. Found C, 48.9; H, 5.3; N, 24.6%.

EXAMPLE 23

2-Chloro-5'-cyano-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by general method A, described in more detail in Example 22. 2',3'-Di-*O*-benzoyl-2-chloro-5'-cyano-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine [prepared from 1-amino-6-phenylthiopiperidine (Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) and 9-(2',3'-di-*O*-benzoyl-5'-cyano-5'-deoxy-ß-D-ribo-furanosyl)-2,6-dichloro-9H-purine as described in Example 24] (1.5 g, 2.5 mmol) in methanol (20 ml) was treated with methanolic ammonia (5 ml). The reaction mixture was stirred at ambient temperature for 0.75 h. Ethyl acetate (5 ml) was added to the residue on evaporation to provide 2-chloro-5'-cyano-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine (0.11 g, 46%) as a solid, m.p. 159-161°C, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.68 (2H, br q, piperidine C-H), 1.98 (2H, m, piperidine C-H), 2.78 (2H, br, piperidine C-H), 3.04 (2H, br d, H-5'$_a$ and H-5'$_b$), 4.11 (2H, m, H-4'and H-3'), 4.63 (1H, m, H-2'), 5.54, 5.68 (2H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 7.22 - 7.45 (5H, 3m, Ar-H), 8.38 (1H, s, H-8), 9.49 (1H, s, N-H). HPLC retention time 20.34 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 96%

at 250 nm).

$C_{16}H_{20}ClN_7O_3$. 0.7 H_2O. 0.1 EtOAc requires C, 51.4; H, 5.1; N, 18.7. Found C, 51.4; H, 4.9; N, 18.3%.

EXAMPLE 24

2-Chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

The title compound was prepared using general method A starting from 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-deoxy-D-ribofuranose prepared according to general method B as follows:

Methyl 2,3-di-*O*-benzoyl-5'-deoxy-D-ribofuranoside

Methyl 5'-deoxy-2,3-*O*-(1-methylethylidene)-D-ribofuranoside (prepared by reduction of methyl 2,3-*O*-(1-methylethylidene)-5'-*O*-(p-toluenesulphonyl)-D-ribofuranoside using lithium aluminium hydride) (4.36 g, 23.2 mmol) was dissolved in methanol (120 ml) and Amberlyst resin (H^+ form, 19 g) was introduced. The mixture was stirred at 80°C for 60 h and filtered. The filter pad was washed with methanol and the filtrate was evaporated to an oily residue. The residue was dissolved in dichloromethane and to this solution was added triethylamine (25.7 g, 185 mmol). Benzoyl chloride (13.08 g, 10.8 ml, 92.8 mmol) was added dropwise over 0.5 h and the reaction mixture was stirred at ambient temperature for 40 h. The reaction mixture was extracted with 0.5 M hydrochloric acid solution (2 x 50 ml) and sodium bicarbonate solution (30 ml) before being dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (4:1), gradually increasing polarity a (1:1) mixture of these solvents, providing the title methyl 2,3-di-*O*-benzoyl-5'-

deoxy-D-ribofuranoside (6.11 g, 74%), ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.50 (3H, d, -CHC<u>H</u>$_3$), 3.48 (3H, s, -COC<u>H</u>$_3$), 4.48 (1H, q), 5.11 (1H, s), 5.46 (1H, t), 5.60 (1H, d), 7.25 - 8.19 (20H, m, Ar-H).

9-(2',3'-Di-*O*-benzoyl-5'-deoxy-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine

1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-deoxy-D-ribofuranose [prepared from the above methyl 2,3-di-*O*-benzoyl-5'-deoxy-D-ribofuranoside by the method described in Lerner, L. Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques, Part Four. Townsend, L.B. and Tipson, R.S., Eds.; John Wiley and Sons, New York, 1991, pp 274 - 280] (1.02 g, 2.65 mmol) and 2,6-dichloro-9H-purine (0.48 g, 2.53 mmol) were mixed thoroughly and heated at 145°C under oilpump vacuum for 2 h. The cooled reaction mixture was dissolved in dichloromethane (25 ml), evaporated, and coevaporated with toluene (2 x 50 ml). Purification of the residue by flash chromatography provided the title 9-(2',3'-di-*O*-benzoyl-5'-deoxy-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.90 g, 58%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.67 (3H, d, -CHC<u>H</u>$_3$), 4.64 (1H, dt, H-4'), 5.72 (1H, t, H-3'), 6.12 (1H, t, H-2'), 6.35 (1H, d , H-1'), 7.31 - 8.05 (10H, m, Ar-H), 8.31 (1H, s, H-8).

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

9-(2',3'-Di-*O*-benzoyl-5'-deoxy-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.46 g, 0.75 mmol) was dissolved in dioxan (10 ml). 1-Aminopiperidine (0.06 ml, 0.90 mmol) and triethylamine (0.16 ml, 1.13 mmol) were added and the reaction mixture was stirred at ambient temperature for 18 h before being evaporated.
The residue was treated with water (50 ml) and ethyl acetate (100 ml). The organic phase was separated and washed with water (2 x 50 ml).

The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (1:1) to provide the title 2,3-di-O-benzoyl-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine (0.30 g, 69%) as a foam, ^{1}H-NMR (400MHz, $CDCl_3$) 1.48 (2H, br, piperidine C-H), 1.80 (2H, m, piperidine C-H), 2.87 (2H, br, piperidine C-H), 4.57 (1H, dt, H-4'), 5.71 (1H, t, H-3'), 6.07 (1H, t, H-2'), 6.33 (1H, d , H-1'), 7.28 - 8.00 (11H, m, Ar-H and H-8).

2-Chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

2,3-Di-*O*-benzoyl-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine (0.30 g, 0.81 mmol) was dissolved in methanol (10 ml) and methanolic ammonia (5 ml) was introduced. The reaction mixture was stirred at ambient temperature for 18 h. and evaporated. The residue was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to provide the title 2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine (0.13 g, 43%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.21 - 1.43 (5H, m, piperidine C-H and CHC$\underline{H}_3$), 1.63 (4H, br q, piperidine C-H), 2.82 (4H, br m, piperidine C-H), 5.79 (1H, d, H-1'), 8.37 (1H, s, H-8), 9.32 (1H, s, N-H). HPLC retention time 6.82 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water).

EXAMPLE 25

2-Chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine

Methyl 5-deoxy-5'-methylene-2,3-*O*-(1-methylethylidene)-D-ribo-furanoside

Triphenylmethylphosphonium bromide (26.79 g, 75 mmol) was suspended in THF (200 ml) and n-butyllithium (1.7M in hexanes) (42 ml, 71.2 mmol) was introduced. After stirring for 2 h, methyl 5-deoxy-5-oxo-2,3-*O*-(1-methylethylidene)-D-ribofuranoside (prepared by oxidation of 1-*O*-methyl-2,3-*O*-(1-methylethylidene)-D-ribofuranoside using the method described in Ranganathan, R.S., Jones, G.H. and Moffatt, J.G., Journal of Organic Chemistry, **1974**, *39(3)*, 290-298) (5.06 g, 25 mmol) in THF (50 ml) was added dropwise. The reaction mixture was heated for 2 h at 50°C and cooled. A mixture of water (10 mL) and THF (90 ml) were added carefully under a stream of nitrogen. Diethyl ether (250 ml) and water (250ml) were introduced. The aqueous phase was washed with diethyl ether (250 ml) and the combined organic extracts were washed with saturated brine (150 ml) and dried ($MgSO_4$). The residue on evaporation was purified by flash chromatography eluting with a mixture of cyclohexane and ethyl acetate (19:1), increasing polarity to a mixture of heptane and ethyl acetate (9:1) provided the desired methyl 5-deoxy-2,3-*O*-(1-methylethylidene)-5-methylene-D-ribofuranoside (3.6 g, 72%) as a gum, ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.32, 1.50 (6H, 2s, $C(CH_3)_2$), 3.36 (3H, s, $-COCH_3$), 4.64 (1H, s), 4.65 (1H, d), 5.00 (1H, s), 5.15 (1H, d), 5.26 (1H, d), 5.83 - 5.92 (1H, m).

Methyl 2,3-di-*O*-benzoyl-5-deoxy-5-methylene-D-ribofuranoside

Methyl 5-deoxy-2,3-*O*-(1-methylethylidene)-5-methylene-D-ribofuranoside (5.65 g, 28.2 mmol) was dissolved in methanol (250 ml) and Amberlyst resin (H^+ form, 30 g) was introduced. The mixture was stirred at ambient temperature for 40 h and was filtered. The filter pad was washed with methanol and the filtrate was evaporated to an oily residue. The residue was dissolved in dichloromethane and to this solution was added benzoyl chloride (8.47 g, 7.0 ml, 60 mmol) and triethylamine (6.49 g, 8.94 ml, 66 mmol) and the reaction mixture was stirred at ambient

temperature for 18 h. The reaction mixture was extracted with 0.5 M hydrochloric acid solution (2 x 100 ml) and water (100 ml) before being dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (29:1), gradually increasing polarity to a (4:1) mixture of these solvents, providing the title methyl 2,3-di-*O*-benzoyl-5-deoxy-5-methylene-D-ribofuranoside (1.66 g, 26%), ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.50 (3H, s, $-COCH_3$), 4.75 - 4.82 (1H, m), 5.16 (1H, s), 5.30 (1H, d), 5.45 (1H, d), 5.61 (1H, d), 5.94 -6.09 (1H, m).

9-(2',3'-Di-*O*-benzoyl-5'-deoxy-5'-methylene-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine

1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-methylene-D-ribofuranose [prepared from the above methyl 2,3-di-*O*-benzoyl-5-deoxy-(1-methylethylidene)-5-methylene-D-ribofuranoside by the method described in Lerner, L. Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques, Part Four. Townsend, L.B. and Tipson, R.S., Eds.; John Wiley and Sons, New York, 1991, pp 274 - 280] (4.2 g, 10.6 mmol) and 2,6-dichloro-9H-purine (2.0 g, 10.6 mmol) were suspended in dichloromethane (25 ml) and evaporated to a residue which was heated at 150°C under oilpump vacuum for 1.5 h. The cooled reaction mixture was dissolved in dichloromethane (25 ml), evaporated, and coevaporated with toluene (2 x 50 ml). Purification of the residue by flash chromatography eluting with a mixture of heptane and ethyl acetate (9:1), increasing polarity to a mixture of heptane and ethyl acetate (4:1) provided the title 2,6-dichloro-9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-9H-purine (3.98 g, 71%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 4.98 (1H, d), 5.48 (1H, d), 5.58 (1H, d), 5.91 (1H, t), 6.16 (1H, t , H-2'), 6.22 (1H, m), 6.44 (1H, d, H-1'), 7.34 - 8.08 (10H, m, Ar-H), 8.34 (1H, s, H-8). HPLC retention

time 15.51 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)-adenosine

2,6-Dichloro-9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-9H-purine (0.3 g, 0.57 mmol) was dissolved in dioxan (20 ml). 1-Aminopiperidine (0.066 g, 0.63 mmol) and triethylamine (0.087 g, 0.12 ml, 0.86 mmol) were added and the reaction mixture was stirred at ambient temperature for 40 h and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (4:1), gradually increasing polarity to a (1:1) mixture of these solvents, to afford the title 2,3-di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine (0.28 g, 83%), ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.93 (1H, dt), 5.43 (1H, dd), 5.56 (1H, d), 5.89 (1H, t), 6.10 (1H, t , H-2'), 6.21 (1H, m), 6.42 (1H, d, H-1'), 7.33 - 8.05 (10H, m, Ar-H).

2-Chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine

2,3-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)-adenosine (0.28 g, 0.47 mmol) was dissolved in methanolic ammonia (10 ml) and stirred at ambient temperature for 18 h. The reaction mixture was evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to provide the title 2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)-adenosine (0.081 g, 45%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.30 - 1.45 (2H, br m, piperidine C-H), 1.62 (4H, br q, piperidine C-H), 2.84 (4H, br, piperidine C-H), 4.07 (1H, dt, H-3'), 4.32 (1H, q, H-2'), 4.58 (1H, m, H-4'), 5.20 (1H, dd, C=C-H), 5.30 (1H, d, C=C-H), 5.40,

5.56 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 6.07 (1H, m, C=C-H), 8.36 (1H, s, H-8), 9.34 (1H, s, N-H). HPLC retention time 9.35 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 99.5% at 250 nm).

EXAMPLE 26

2-Chloro-5'-deoxy-5'-methylene-*N*-(4-phenylthio-1-piperidinyl)adenosine

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(4-phenylthio-1-piperidinyl)adenosine, prepared as described in Example 25 from 2,6-dichloro-9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-9H-purine (1.0 g, 1.9 mmol) and 1-amino-4-phenylthiopiperidine (0.44 g, 2.1 mmol), was dissolved in methanol (20 ml) and sat. methanolic ammonia (2.5 ml) was introduced. The reaction mixture was stirred at ambient temperature for 18 h, evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and ethanol (50:1) to provide the title 2-chloro-5'-deoxy-5'-methylene-*N*-(4-phenylthio-1-piperidinyl)adenosine (0.27 g, 29%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.70 (2H, br q, piperidine C-H), 1.99 (2H, br d, piperidine C-H), 2.77 (2H, br m, piperidine C-H), 3.06 (2H, br m, piperidine C-H), 4.07 (1H, q, H-3'), 4.32 (1H, dt, H-2'), 4.58 (1H, m, H-4'), 5.20 (1H, dd, C=C-H), 5.29 (1H, d, C=C-H), 5.39, 5.56 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 6.07 (1H, m, C=C-H), 7.23 - 7.45 (5H, 3 m, Ar-H), 8.36 (1H, s, H-8), 9.34 (1H, s, N-H). HPLC retention time 13.46 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 100% at 250 nm).

EXAMPLE 27

2-Chloro-5'-deoxy-*N*-methoxy-5'-methyleneadenosine

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-*N*-methoxy-5'-methyleneadenosine (0.2 g, 0.4 mmol), prepared by the method described in Example 25 from 2,6-dichloro-9-(2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-9H-purine (0.5 g, 2.0 mmol) and *O*-methylhydroxlamine hydrochloride (0.167 g, 2.0 mmol), was treated with methanolic ammonia (10 ml) and stirred at ambient temperature for 18 h. The reaction mixture was evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (19:1) to provide the title 2-chloro-5'-deoxy-*N*-methoxy-5'-methyleneadenosine (0.03 g, 9%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 3.79 (3H, s, -CH_3), 4.08 (1H, q, H-3'), 4.33 (1H, dt, H-2'), 4.61 (1H, m, H-4'), 5.20 (1H, dd, C=C-H), 5.31 (1H, d, C=C-H), 5.42, 5.59 (2H, 2d, 2'-and 3'-OH), 5.89 (1H, d, H-1'), 6.08 (1H, m, C=C-H), 8.44 (1H, s, H-8), 11.58 (1H, s, N-H). HPLC retention time 7.09 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 98.6% at 250 nm).

EXAMPLE 28

2-Chloro-5'-deoxy-5'-methylene-*N*-cyclopentyladenosine

2,3-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-cyclopentyladenosine (prepared by reaction of 2,6-dichloro-9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-9H-purine with cyclopentylamine) (0.30 g, 0.52 mmol) was dissolved in methanolic ammonia (10 ml) and stirred at ambient temperature for 18 h. The reaction mixture was evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (39:1) to provide the title

2-chloro-5'-deoxy-5'-methylene-*N*-cyclopentyladenosine (0.051 g, 27%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) δ 1.48 - 2.04 (8H, 3 br m, cyclopentyl C-H), 4.08 (1H, q, H-3'), 4.32 (1H, dt, H-2'), 4.42 (1H, m, -HN-C-H), 4.59 (1H, m, H-4'), 5.19 (1H, dd, C=C-H), 5.30 (1H, d, C=C-H), 5.40, 5.55 (2H, 2d, 2'-and 3'-OH), 5.85 (1H, d, H-1'), 6.08 (1H, m, C=C-H), 8.34 (1H, s & br s, H-8 and N-H).

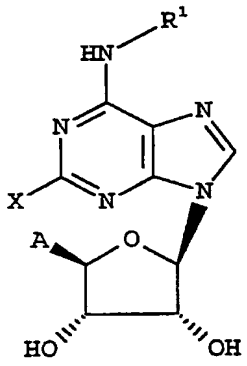
EXAMPLE 29

5'-Deoxy-2,5'-dichloro-*N*-(4-phenylthiocyclohexyl)adenosine

This compound was prepared by general method C, described in more detail in Example 2. 2-Chloro-*N*-(4-phenylthiocyclohexyl)adenosine (prepared from 4-hydroxycyclohexlamine by the general methods laid out in Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) (0.2 g, 0.44 mmol) was subjected to the reaction conditions described above, and the residue on evaporation was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (4:1), gradually increasing polarity to a (19:1) mixture of ethyl acetate and methanol to afford the title 5'-deoxy-2,5'-dichloro-*N*-(4-phenylthiocyclohexyl)-adenosine (0.08 g, 38%), ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.20 - 1.30 (2H, t, cyclohexyl C-H), 1.80 - 2.05 (6H, br m, cyclohexyl C-H), 3.75 - 3.84 (2H, m, H-5'$_a$ and H-5'$_b$), 5.96 (1H, d, H-1'), 7.19 - 7.33 (3H, m, Ar-H), 7.41 (2H, d, Ar-H), 7.99 (1H, s, H-8), 8.29 (1H, s, N-H). HPLC retention time 9.1 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 100% purity at 250 nm).

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof



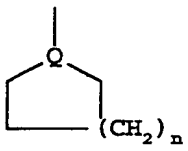
(I)

wherein

X is halogen, amino, perhalomethyl, cyano, C_{1-6}-alkoxy, C_{1-6}-alkylthio or C_{1-6}-alkylamino;

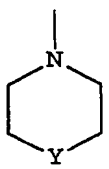
A is methyl, halomethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

R^1 is selected from the groups consisting of



(a)

wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylsulphinyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, phenylthioalkyl or



(b)

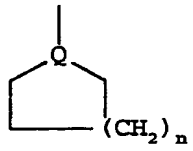
wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,
wherein Y is oxygen or sulphur;
R^2 is C_{1-6}-alkyl;
R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;
R^4 is C_{1-6}-alkyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy.

2. A compound of claim 1, wherein
X is halogen, amino, C_{1-6}-alkylthio or C_{1-6}-alkylamino;

A is methyl, halomethyl, cyanomethyl, vinyl, methylthiomethyl or methoxymethyl;

R^1 is



(a)

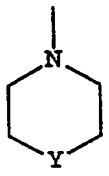
wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl,phenylsulphinyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, phenylthioalkyl.

3. A compound of claim 1, wherein
X is halogen, amino, C_{1-6}-alkylthio or C_{1-6}-alkylamino;

A is methyl, halomethyl, cyanomethyl, vinyl, methylthiomethyl or meth-

oxymethyl;

R^1 is



(b)

wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl.

4. A compound of claim 1, wherein

X is halogen, amino, C_{1-6}-alkylthio or C_{1-6}-alkylamino;

A is methyl, halomethyl, cyanomethyl, vinyl, methylthiomethyl or methoxymethyl;

R^1 is $-NR^2R^3$ or $-YR^4$,

wherein Y is oxygen or sulphur;

R^2 is C_{1-6}-alkyl;

R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;

R^4 is C_{1-6}-alkyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy.

5. A pharmaceutical composition comprising as active component a compound according to claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition according to claim 5 in the form of an oral dosage unit containing about 1-200 mg of the active compound.

7. A method of treating a central nervous system ailment in a person in need of such treatment characterized in administering to said person an amount of a compound of claim 1 effective in alleviation of such an ailment.

8. A method of treating a central nervous system ailment in a subject in need of such treatment comprising the step of administering to said subject an amount of a compound of claim 1 which is effective for the alleviation of such ailment in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00344

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07H 19/16, C07H 19/167, A61K 31/70
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07H, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO, A1, 9323417 (NOVO NORDISK A/S), 25 November 1993 (25.11.93) --	1-6
X	WO, A1, 9308206 (NOVO NORDISK A/S), 29 April 1993 (29.04.93) --	1-6
Y	EP, A2, 0232813 (WARNER-LAMBERT COMPANY), 19 August 1987 (19.08.87) --	1-6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 1994	28 -12- 1994
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00344

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	STN International, File CA, Chemical Abstracts, volume 103, no. 19, 11 November 1985 (Columbus Ohio, US), Kusachi Shozo et al: "Dog coronary artery adenosine receptor: structure of the N6-alkyl subregion", abstract no. 153334g, & J. Med. Chem., 28(11), 1636-43	1-6
Y	STN International, File CA, Chemical Abstracts, volume 79, no. 19, 12 November 1973 (Columbus, Ohio, US), Fujii, Tozo et al: "Purines. XII. Catalytic hydrogenolysis of alkoxyaminopurines and related derivatives", abstract no. 115832w, & Chem. Pharm. Bull., 21(8), 1835-8	1-6
Y	STN International, File CA, Chemical Abstracts, volume 79, no. 17, 29 October 1973 (Columbus Ohio, US), Fujii, Tozo et al: "Purines. XI. Sunthesis of N-alkoxyadenosines and their 2', 3'-O-isopropylidene derivatives", abstract no. 105513d, & Chem. Pharm. Bull., 21(8), 1676-82	1-6
Y	STN International, File CA, Chemical Abstracts, volume 69, no. 13, 23 September 1968 (Columbus Ohio, US), Giner-Sorolla, A. et al: "The synthesis and biological properties of hydroxylaminopurines and related derivatives", abstract no. 52103e, & J. Med. Chem., 11(3), 521-3	1-6
Y	WO, A1, 8504882 (NELSON RESEARCH AND DEVELOPMENT COMPANY), 7 November 1985 (07.11.85)	1-6
A	DE, A, 1545645 (BOEHRINGER MANNHEIM GMBH), 21 August 1969 (21.08.69)	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 94/00344

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7, 8
because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

26/11/94

International application No.
PCT/DK 94/00344

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A1- 9323417	25/11/93	NONE		
WO-A1- 9308206	29/04/93	CA-A-	2121844	29/04/93
		EP-A-	0609375	10/08/94
		FI-A,D-	941876	22/06/94
EP-A2- 0232813	19/08/87	AU-B-	592728	18/01/90
		AU-A-	6797287	06/08/87
		CA-A-	1270821	26/06/90
		JP-A-	62228095	06/10/87
		US-A-	4755594	05/07/88
WO-A1- 8504882	07/11/85	AU-B-	582359	23/03/89
		AU-A-	4219585	15/11/85
		CA-A-	1293721	31/12/91
		CA-A-	1293722	31/12/91
		CA-A-	1305135	14/07/92
		DE-D,T-	3587717	28/04/94
		EP-A,B-	0180614	14/05/86
		SE-T3-	0180614	
		EP-A-	0300144	25/01/89
		EP-A-	0300145	25/01/89
		EP-A,B-	0305643	08/03/89
		JP-T-	61501914	04/09/86
		US-A-	5043325	27/08/91
DE-A- 1545645	21/08/69	CH-A-	486487	28/02/70
		CH-A-	491952	15/06/70
		FR-A-	1503243	00/00/00
		GB-A-	1101108	00/00/00
		NL-A-	6617087	07/06/67
		US-A-	3475408	28/10/69